4-14-97

L10 ANSWER 2 OF 6 CAPLUS COPYRIGHT 1997 ACS
AN 1996:693923 CAPLUS
DN 126:114991
TI Expression, characterization, and mutagenesis of the aspartic proteinase from equine infectious anemia virus
AU Powell, David J.; Bur, Daniel; Wlodawer, Alexander; Gustchina, Alla; Payne, Susan L.; Dunn, Ben M.; Kay, John
CS College Cardiff, Univ. Wales, Cardiff, CF1 3US, UK
SO Eur. J. Biochem. (1996), 241(2), 664-674
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English
AB The gene encoding the proteinase from equine infectious anemia virus (EIAV) was cloned and expressed in Escherichia coli. The recombinant EIAV proteinase was purified to homogeneity and shown to have the ability to process polyprotein and synthetic peptide substrates of human immunodeficiency virus (HIV) origin with an efficiency that can approach that exhibited by HIV proteinase. EIAV proteinase, however, was not susceptible to inhibition by a wide variety of inhibitors HIV-1 proteinase, including those which have been licensed as anti-AIDS drugs. In this respect, EIAV proteinase behaves like an extreme case of a drug-resistant mutant of HIV-1 proteinase that has arisen under selective drug pressure. Only one potent inhibitor (HBY-793) of HIV-1 proteinase showed comparable efficiency against the EIAV enzyme; the compds. **A-77003** and A-76889, which differ only in their stereochem. and which are otherwise structurally identical to HBY-793 from residues P2 to P2' [nomenclature of Schechter, I. & Berger, A. (1967) Biochem. Biophys. Res. Commun. 27, 157-162], were not effective inhibitors of EIAV proteinase. Mutant forms of EIAV proteinase (Thr30.fwdarw.Asp and Ile54.fwdarw.Gly) were generated and their ability to interact with substrates and inhibitors was characterized. HBY-793 inhibited [Gly54]proteinase as effectively as the wild-type proteinase but was tenfold less potent against [Asp30]proteinase. Data interpretations are presented, based on the structure solved for the complex between HBY-793 and EIAV [Gly54]proteinase [Gustchina A., Kervinen, J., Powell, D. J., Zdanov, A., Kay, J. & Wlodawer, A. (1996) Protein Sci. 5, 1453-1465].

L10 ANSWER 3 OF 6 CAPLUS COPYRIGHT 1997 ACS
AN 1996:228484 CAPLUS
DN 124:290277
TI HIV protease inhibitor combinations.
IN Barrish, Joel C.; Colonno, Richard J.; Lin, Pin-Fang M.
PA Bristol-Myers Squibb Co., USA
SO Eur. Pat. Appl., 29 pp.
CODEN: EPXXDW
PI EP 691345 A2 960110
DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
AI EP 95-304718 950705
PRAI US 94-270614 940705
US 95-436868 950517
DT Patent
LA English
AB A product comprising HIV-1 protease inhibitor (I) (BMS-186318) and .gtoreq.1 of RO 31-8959, SC-52151, **A-77003**, A-80987, ABT-538, L-735,524, and AG-1343 is claimed. The

combinations may eliminate or substantially reduce viral cross-resistance seen with use of individual HIV-1 protease inhibitors. A synthesis of I via coupling of epoxide (II) with aminoalc. (III) is given.

L10 ANSWER 4 OF 6 CAPLUS COPYRIGHT 1997 ACS
AN 1996:153437 CAPLUS
DN 124:220480
TI Retroviral protease inhibitor combinations
IN Bryant, Martin L.; Potts, Karen E.; Smidt, Mary; Tucker, Simon P.
PA G.D. Searle and Co., USA
SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
PI WO 9533464 A2 951214
DS W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-US6673 950602
PRAI US 94-253638 940603
DT Patent
LA English
AB A method is disclosed for the treatment of mammalian retrovirus infections, e.g. HIV, using combinations of retroviral protease inhibitors which are effective in preventing the replication of the retroviruses in vitro or in vivo. In particular, the invention provides protease inhibitor compds. used in combination therapy with other protease inhibitor compds. Also disclosed is combination therapy with a combination of protease inhibitors and antiviral agents other than protease inhibitors. Prepn. and activity of selected inhibitors is included.

L10 ANSWER 5 OF 6 CAPLUS COPYRIGHT 1997 ACS
AN 1996:124703 CAPLUS
DN 124:196942
TI Design, synthesis, and resistance patterns of MP-134 and MP-167, two novel inhibitors of HIV type 1 protease
AU Mo, Hongmei; Markowitz, Martin; Majer, Pavel; Burt, Stanley K.; Gulnik, Sergei V.; Suvorov, Leonard I.; Erickson, John W.; Ho, David D.
CS School Medicine, New York University, New York, NY, 10016, USA
SO AIDS Res. Hum. Retroviruses (1996), 12(1), 55-61
CODEN: ARHRE7; ISSN: 0889-2229
DT Journal
LA English
AB Inhibitors of HIV-1 protease represent a new class of antiretroviral compds. This report describes the design and synthesis of 2 novel C2 symmetry-based inhibitors, MP-134 (I) and MP-167 (II), specifically targeted against HIV-1 variants with reduced sensitivity to another related protease inhibitor, **A-77003**. In addn., the in vitro selection of viral variants with reduced sensitivity to these 2 protease inhibitors is described. An isoleucine-to-valine substitution at residue 84 (I84V) of the HIV-1 protease confers resistance to MP-134, whereas a glycine-to-valine substitution at residue 48 (G48V) confers resistance to MP-167. Testing other protease inhibitors against these variants has revealed specific overlapping patterns of resistance among these agents. These findings have important implications in the design of combination regimens using multiple protease inhibitors and underscore the need to develop non-cross-resistant compds. to be used toward this goal.

L10 ANSWER 6 OF 6 CAPLUS COPYRIGHT 1997 ACS
AN 1995:683314 CAPLUS

DN 123:102100

TI Kinetic Characterization and Cross-Resistance Patterns Of HIV-1 Protease Mutants Selected under Drug Pressure

AU Gulnik, Sergei V.; Suvorov, Leonid I.; Liu, Beishan; Yu, Betty; Anderson, Barry; Mitsuya, Hiroaki; Erickson, John W.

CS Frederick Cancer Research and Development Center, National Cancer Institute, Frederick, MD, 21702-1201, USA

SO Biochemistry (1995), 34(29), 9282-7
CODEN: BICHAW; ISSN: 0006-2960

DT Journal

LA English

OS CJACS

AB Eleven different recombinant, drug-resistant HIV-1 protease (HIV PR) mutants-R8Q, V32I, M46I, V82A, V82F, V82I, I84V, V32I/I84V, M46I/V82F, M46I/I84V, and V321/K45I/F53L/A71V/I84V/L89M-were generated on the basis of results of in vitro selection expts. using the inhibitors **A-77003**, A-84538, and KNI-272. Kinetic parameters of mutant and wild-type (WT) enzymes were measured along with inhibition consts. (Ki) toward the inhibitors **A-77003**, A-84538, KNI-272, L-735,524, and Ro31-8959. The catalytic efficiency, kcat/Km, for the mutants decreased relative to WT by a factor of 1.2-15 and was mainly due to the elevation of Km. The effects of specific mutations on Ki values were unique with respect to both inhibitor and mutant enzyme. A new property, termed vitality, defined as the ratio (Kikcat/Km)mutant/(Kikcat/Km)WT was introduced to compare the selective advantage of different mutants to an inhibitor. High vitality values were generally obsd. with mutations that emerged during in vitro selection studies. The kinetic model along with the panel of mutants described here should be useful for evaluating and predicting patterns of resistance for HIV PR inhibitors and may aid in the selection of inhibitor combinations to combat drug resistance.

L11 ANSWER 2 OF 2 CAPLUS COPYRIGHT 1997 ACS
AN 1996:228484 CAPLUS
DN 124:290277
TI HIV protease inhibitor combinations.
IN Barrish, Joel C.; Colonno, Richard J.; Lin, Pin-Fang M.
PA Bristol-Myers Squibb Co., USA
SO Eur. Pat. Appl., 29 pp.
CODEN: EPXXDW
PI EP 691345 A2 960110
DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
AI EP 95-304718 950705
PRAI US 94-270614 940705
US 95-436868 950517
DT Patent
LA English
AB A product comprising HIV-1 protease inhibitor (I) (BMS-186318) and .gtoreq.1 of RO 31-8959, SC-52151, A-77003, A-80987, ABT-538, L-735,524, and AG-1343 is claimed. The combinations may eliminate or substantially reduce viral cross-resistance seen with use of individual HIV-1 protease inhibitors. A synthesis of I via coupling of epoxide (II) with aminoalc. (III) is given.

L12 ANSWER 2 OF 2 CAPLUS COPYRIGHT 1997 ACS
AN 1996:124703 CAPLUS
DN 124:196942
TI Design, synthesis, and resistance patterns of MP-134 and MP-167, two novel inhibitors of HIV type 1 protease
AU Mo, Hongmei; Markowitz, Martin; Majer, Pavel; Burt, Stanley K.; Gulnik, Sergei V.; Suvorov, Leonard I.; Erickson, John W.; Ho, David D.
CS School Medicine, New York University, New York, NY, 10016, USA
SO AIDS Res. Hum. Retroviruses (1996), 12(1), 55-61
CODEN: ARHRE7; ISSN: 0889-2229
DT Journal
LA English
AB Inhibitors of HIV-1 protease represent a new class of antiretroviral compds. This report describes the design and synthesis of 2 novel C2 symmetry-based inhibitors, MP-134 (I) and MP-167 (II), specifically targeted against HIV-1 variants with reduced sensitivity to another related protease inhibitor, A-77003. In addn., the in vitro selection of viral variants with reduced sensitivity to these 2 protease inhibitors is described. An isoleucine-to-valine substitution at residue 84 (I84V) of the HIV-1 protease confers resistance to MP-134, whereas a glycine-to-valine substitution at residue 48 (G48V) confers resistance to MP-167. Testing other protease inhibitors against these variants has revealed specific overlapping patterns of resistance among these agents. These findings have important implications in the design of combination regimens using multiple protease inhibitors and underscore the need to develop non-cross-resistant compds. to be used toward this goal.

L13 ANSWER 2 OF 7 CAPLUS COPYRIGHT 1997 ACS
AN 1997:91000 CAPLUS
DN 126:180865
TI Resistance-related mutations in the HIV-1 protease gene of patients treated for 1 year with the protease inhibitor ritonavir (ABT-538)
AU Schmit, Jean-Claude; Ruiz, Lidia; Clotet, Bonaventura; Raventos, Antoni; Tor, Jordi; Leonard, John; Desmyter, Jan; De Clercq, Erik; Vandamme, Anne-Mieke
CS AIDS Research Unit, Rega Institute for Medical Research, Minderbroedersstraat, Louvain, Belg.
SO AIDS (London) (1996), 10(9), 995-999
CODEN: AIDSET; ISSN: 0269-9370
DT Journal
LA English
AB The objective of this study was to define genotypic and phenotypic resistance patterns following prolonged therapy with the protease inhibitor ritonavir (ABT-538). Seven HIV-1-infected patients, all but one previously treated with dideoxynucleoside analogs (zidovudine, didanosine, zalcitabine), were treated for 1 yr with ritonavir. Direct solid-phase sequencing of the protease gene starting from plasma derived viral RNA followed by comparison to phenotypic drug resistance data. The most frequent amino acid substitutions occurring upon administration of the protease inhibitor were V82A/F (substrate binding site), I54V (flap region), A71V and L10I. Addnl. mutations found in more than one patient were I15V, M36I, I84V and I93L. Mutation L63P was found both in pre- and post-ritonavir samples. Phenotypic drug resistance assays confirmed resistance to ritonavir in post-treatment samples (.apprx.170-fold) and showed cross-resistance to indinavir (.apprx.30-fold) and partially to **saquinavir** (.apprx.fivefold). At 1 yr of treatment, one patient without known resistance-assocd. mutations in the protease gene still showed a substantial rise in CD4 cell count accompanied by a more than 2.4 log decrease in RNA viral load. However, at week 78, mutations R8Q, E34K, R57K, L63P and I84V were detected and the treatment benefit was partially lost. Long-term treatment with ritonavir is assocd. with the emergence of multiple mutations in the HIV-1 protease gene. The mutations L10I, I54V, L63P, A71V, V82A/F and I84V correspond to known drug-resistance mutations for ritonavir and other protease inhibitors. Phenotypic resistance to ritonavir was detected in a majority of ritonavir-treated patients at 1 yr of treatment. In addn., long-term ritonavir treatment selects for cross-resistance to the protease inhibitors indinavir and **saquinavir**. This argues against sequential therapy with several protease inhibitors. Delayed resistance in one patient was accompanied with a prolonged increase in CD4 cell count and decrease in viral load suggesting a temporary benefit of treatment.

L13 ANSWER 3 OF 7 CAPLUS COPYRIGHT 1997 ACS
AN 1997:21630 CAPLUS
DN 126:112776
TI Mutational anatomy of an HIV-1 protease variant conferring cross-resistance to protease inhibitors in clinical trials. Compensatory modulations of binding and activity
AU Schock, Hilary B.; Garsky, Victor M.; Kuo, Lawrence C.
CS Dep. Antiviral Res., Merck Res. Lab., West Point, PA, 19486, USA
SO J. Biol. Chem. (1996), 271(50), 31957-31963
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal

LA English

AB Site-specific substitutions of as few as four amino acids (M46I/L63P/V82T/I84V) of the human immunodeficiency virus type 1 (HIV-1) protease engenders cross-resistance to a panel of protease inhibitors that are either in clin. trials or have recently been approved for HIV therapy (Condra, J. H., Schleif, W. A., Blahy, O. M., Gadryelski, L. J., Graham, D. J., Quintero, J. C., Rhodes, A., Robbins, H. L., Roth, E., Shivaprakash, M., Titus, D., Yang, T., Teppler, H., Squires, K. E., Deutsch, P. J., and Emini, E. A. (1995) Nature 374, 569-571). These four substitutions are among the prominent mutations found in primary HIV isolates obtained from patients undergoing therapy with several protease inhibitors. Two of these mutations (V82T/I84V) are located in, while the other two (M46I/L63P)are away from, the binding cleft of the enzyme. The functional role of these mutations has now been delineated in terms of their influence on the binding affinity and catalytic efficiency of the protease. The authors have found that the double substitutions of M46I and L63P do not affect binding but instead endow the enzyme with a catalytic efficiency significantly exceeding (110-360%) that of the wild-type enzyme. In contrast, the double substitutions of V82T and I84V are detrimental to the ability of the protease to bind and, thereby, to catalyze. When combined, the four amino acid replacements institute in the protease resistance against inhibitors and a significantly higher catalytic activity than one contg. only mutations in its active site. The results suggest that in raising drug resistance, these four site-specific mutations of the protease are compensatory in function; those in the active site diminish equil. binding(by increasing Ki), and those away from the active site enhance catalysis (by increasing kcat/KM). This conclusion is further supported by energy ests. in that the Gibbs free energies of binding and catalysis for the quadruple mutant are quant. dictated by those of the double mutants.

L13 ANSWER 4 OF 7 CAPLUS COPYRIGHT 1997 ACS

AN 1997:21283 CAPLUS

DN 126:112768

TI Human immunodeficiency virus. Mutations in the viral protease that confer resistance to **saquinavir** increase the dissociation rate constant of the protease-**saquinavir** complex

AU Maschera, Barbara; Darby, Graham; Palu, Giorgio; Wright, Lois L.; Tisdale, Margaret; Myers, Richard; Blair, Edward D.; Furfine, Eric S.

CS Dep. of Molecular Biochemistry, Glaxo Wellcome, Research Triangle Park, NC, 27709, USA

SO J. Biol. Chem. (1996), 271(52), 33231-33235
CODEN: JBCHA3; ISSN: 0021-9258

DT Journal

LA English

AB Mutations in the human immunodeficiency virus (HIV) protease (L90M, G48V, and L90M/G48V) arise when HIV is passaged in the presence of HIV protease inhibitor **saquinavir**. These mutations yield a virus with less sensitivity to the drug (L90M > G48V .mchgt. L90M/G48V). L90M, G48V, and L90M/G48V proteases have 1/20, 1/160, and 1/1000 the affinity for **saquinavir** compared to WT protease, resp. Therefore, the affinity of mutant protease for **saquinavir** decreased as the sensitivity of the virus to **saquinavir** decreased. Assocn. rate consts. for WT and mutant proteases with **saquinavir** were similar, ranging from 2 to 4.times.107 M-1 -1. In contrast, the dissocn. rate consts. for Wt, L90M, G48V, and L90M/G48V proteases complexed with **saquinavir** were 0.0014, 0.019, 0.128, and 0.54 s-1, resp. This indicated that the reduced affinity for mutant proteases and **saquinavir** is primarily the result of larger dissocn. rate consts. The increased dissocn. rate consts. may be the result of a decrease in the internal equil. between the bound inhibitor with the protease flaps up and the bound inhibitor with the flaps down.

Interestingly, the affinity of these mutant proteases for VX-478, ABT-538, AG-1343, or L-735,524 was not reduced as much as that for **saquinavir**. Finally, the catalytic consts. of Wt and mutant proteases were detd. for eight small peptide substrates that mimic the viral cleavage sites in vivo. WT and L90M proteases had similar catalytic consts. for these substrates. In contrast, G48V and L90M/G48V proteases had catalytic efficiency (kcat/Km) values with TLNF-PISP, RKIL-FLDG, and AETF-YVDG that were 1/10 to 1/20 the value of WT protease. The decreased catalytic efficiencies were primarily the result of increased Km values. Thus, mutations in the protease decrease the affinity of the enzyme for **saquinavir** and the catalytic efficiency with peptide substrates.

L13 ANSWER 5 OF 7 CAPLUS COPYRIGHT 1997 ACS
AN 1996:693956 CAPLUS
DN 126:139294
TI HIV-Protease inhibitors. A new class of substances in antiretroviral therapy
AU Mauss, S.; Seidlitz, B.; Jablonowski, H.; Haeussinger, D.
CS Klinik Gastroenterologie Hepatologie Infektiologie, Univ. Duesseldorf, Duesseldorf, D-40225, Germany
SO Dtsch. Med. Wochenschr. (1996), 121(44), 1369-1374
CODEN: DMWOAX; ISSN: 0012-0472
DT Journal; General Review
LA German
AB A review with 33 refs. on the HIV-protease inhibitors **saquinavir**, ritonavir, and indinavir.

L13 ANSWER 6 OF 7 CAPLUS COPYRIGHT 1997 ACS
AN 1996:642100 CAPLUS
DN 125:315866
TI Ritonavir
AU Lea, Andrew P.; Faulds, Diana
CS Adis International Limited, Auckland, N. Z.
SO Drugs (1996), 52(4), 541-546
CODEN: DRUGAY; ISSN: 0012-6667
DT Journal; General Review
LA English
AB A review with .apprx.37 refs. Ritonavir is a protease inhibitor with an HIV-1 resistance profile similar to that of indinavir, but different from that of **saquinavir**. Ritonavir has good oral bioavailability, and may increase the bioavailability of other protease inhibitors including **saquinavir**, nelfinavir, indinavir and VX-478. Clin. significant drug interactions have been predicted between ritonavir and a range of medications. In patients with HIV-1 infection, ritonavir markedly reduced viral load within 2 wk of treatment onset and also increased CD4+ cell counts. In a large placebo-controlled trial in patients with advanced HIV infection, the addn. of ritonavir to existing therapy reduced the risk of mortality by 43% and clin. progression by 56% after 6.1 mo. Triple therapy with ritonavir plus zidovudine, in combination with lamivudine or zalcitabine, reduced HIV viremia to below detectable levels in most patients with acute, and some patients with advanced HIV infection in 2 small trials. Early results suggest combination therapy with ritonavir and **saquinavir** increases CD4+ cell counts and decreases HIV RNA levels in patients with previously untreated HIV infection.

L13 ANSWER 7 OF 7 CAPLUS COPYRIGHT 1997 ACS
AN 1996:601709 CAPLUS
DN 125:238651
TI Use of quinoxalines and protease inhibitors in a composition for the treatment of AIDS and/or HIV infections
IN Paessens, Arnold; Blunck, Martin; Riess, Guenther; Kleim, Joerg-Peter; Roesner, Manfred
PA Bayer A.-G., Germany

SO Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
PI EP 728481 A2 960828
DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
AI EP 96-102129 960214
PRAI DE 95-19506742 950227
DT Patent
LA German
OS MARPAT 125:238651
AB Combinations of a quinoxaline deriv. [I; R1 = halo, OH, NO2, (substituted) amino, N3, CF3, CF3O, C1-8 alkyl, CN, (substituted) Ph, N-heterocyclyl, etc.; R2, R5 = H, OH, C1-6 alkoxy, aryloxy, C1-6 acyloxy, CN, (substituted) amino, (substituted) C1-8 alkyl, (substituted) C2-8 alkenyl, (substituted) C3-8 alkynyl, (substituted) C3-8 cycloalk(en)yl, etc.; R3, R4 = H, (substituted) C1-8 alkyl, (substituted) C2-8 alkenyl, (substituted) C3-8 cycloalk(en)yl, (substituted)aryl, etc.; or R3R4 or R3R5 complete a (substituted) ring; X = O, S, Se, NR2; n = 0-4] and a peptidomimetic protease inhibitor are useful for treatment of HIV infections and AIDS. Thus, I [R1 = 6-MeO, R2 = R3 = H, R4 = (S)-MeSCH2, R5 = i-PrO2C, X = S] (0.7-6 nM) and **saquinavir** (6-50 nM) synergistically inhibited syncytium formation in HIV-infected human

L14 ANSWER 2 OF 5 CAPLUS COPYRIGHT 1997 ACS
AN 1997:21630 CAPLUS
DN 126:112776
TI Mutational anatomy of an HIV-1 protease variant conferring cross-resistance to protease inhibitors in clinical trials. Compensatory modulations of binding and activity
AU Schock, Hilary B.; Garsky, Victor M.; Kuo, Lawrence C.
CS Dep. Antiviral Res., Merck Res. Lab., West Point, PA, 19486, USA
SO J. Biol. Chem. (1996), 271(50), 31957-31963
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Site-specific substitutions of as few as four amino acids (M46I/L63P/V82T/I84V) of the human immunodeficiency virus type 1 (HIV-1) protease engenders cross-resistance to a panel of protease inhibitors that are either in clin. trials or have recently been approved for HIV therapy (Condra, J. H., Schleif, W. A., Blahy, O. M., Gadryelski, L. J., Graham, D. J., Quintero, J. C., Rhodes, A., Robbins, H. L., Roth, E., Shivaprakash, M., Titus, D., Yang, T., Teppler, H., Squires, K. E., Deutsch, P. J., and Emini, E. A. (1995) Nature 374, 569-571). These four substitutions are among the prominent mutations found in primary HIV isolates obtained from patients undergoing therapy with several protease inhibitors. Two of these mutations (V82T/I84V) are located in, while the other two (M46I/L63P)are away from, the binding cleft of the enzyme. The functional role of these mutations has now been delineated in terms of their influence on the binding affinity and catalytic efficiency of the protease. The authors have found that the double substitutions of M46I and L63P do not affect binding but instead endow the enzyme with a catalytic efficiency significantly exceeding (110-360%) that of the wild-type enzyme. In contrast, the double substitutions of V82T and I84V are detrimental to the ability of the protease to bind and, thereby, to catalyze. When combined, the four amino acid replacements institute in the protease resistance against inhibitors and a significantly higher catalytic activity than one contg. only mutations in its active site. The results suggest that in raising drug resistance, these four site-specific mutations of the protease are compensatory in function; those in the active site diminish equil. binding(by increasing Ki), and those away from the active site enhance catalysis (by increasing kcat/KM). This conclusion is further supported by energy ests. in that the Gibbs free energies of binding and catalysis for the quadruple mutant are quant. dictated by those of the double mutants.

L14 ANSWER 3 OF 5 CAPLUS COPYRIGHT 1997 ACS
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DN 126:112768
TI Human immunodeficiency virus. Mutations in the viral protease that confer resistance to saquinavir increase the dissociation rate constant of the protease-saquinavir complex
AU Maschera, Barbara; Darby, Graham; Palu, Giorgio; Wright, Lois L.; Tisdale, Margaret; Myers, Richard; Blair, Edward D.; Furfine, Eric S.
CS Dep. of Molecular Biochemistry, Glaxo Wellcome, Research Triangle Park, NC, 27709, USA
SO J. Biol. Chem. (1996), 271(52), 33231-33235
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English

AB Mutations in the human immunodeficiency virus (HIV) protease (L90M, G48V, and L90M/G48V) arise when HIV is passaged in the presence of HIV protease inhibitor saquinavir. These mutations yield a virus with less sensitivity to the drug (L90M > G48V .mchgt. L90M/G48V). L90M, G48V, and L90M/G48V proteases have 1/20, 1/160, and 1/1000 the affinity for saquinavir compared to WT protease, resp. Therefore, the affinity of mutant protease for saquinavir decreased as the sensitivity of the virus to saquinavir decreased. Assocn. rate consts. for WT and mutant proteases with saquinavir were similar, ranging from 2 to 4.times.107 M-1 -1. In contrast, the dissocn. rate consts. for Wt, L90M, G48V, and L90M/G48V proteases complexed with saquinavir were 0.0014, 0.019, 0.128, and 0.54 s-1, resp. This indicated that the reduced affinity for mutant proteases and saquinavir is primarily the result of larger dissocn. rate consts. The increased dissocn. rate consts. may be the result of a decrease in the internal equil. between the bound inhibitor with the protease flaps up and the bound inhibitor with the flaps down. Interestingly, the affinity of these mutant proteases for **VX -478**, ABT-538, AG-1343, or L-735,524 was not reduced as much as that for saquinavir. Finally, the catalytic consts. of Wt and mutant proteases were detd. for eight small peptide substrates that mimic the viral cleavage sites in vivo. WT and L90M proteases had similar catalytic consts. for these substrates. In contrast, G48V and L90M/G48V proteases had catalytic efficiency (kcat/Km) values with TLNF-PISP, RKIL-FLDG, and AETF-YVDG that were 1/10 to 1/20 the value of WT protease. The decreased catalytic efficiencies were primarily the result of increased Km values. Thus, mutations in the protease decrease the affinity of the enzyme for saquinavir and the catalytic efficiency with peptide substrates.

L14 ANSWER 4 OF 5 CAPLUS COPYRIGHT 1997 ACS
AN 1996:642100 CAPLUS
DN 125:315866
TI Ritonavir
AU Lea, Andrew P.; Faulds, Diana
CS Adis International Limited, Auckland, N. Z.
SO Drugs (1996), 52(4), 541-546
CODEN: DRUGAY; ISSN: 0012-6667
DT Journal; General Review
LA English
AB A review with .apprx.37 refs. Ritonavir is a protease inhibitor with an HIV-1 resistance profile similar to that of indinavir, but different from that of saquinavir. Ritonavir has good oral bioavailability, and may increase the bioavailability of other protease inhibitors including saquinavir, nelfinavir, indinavir and **VX-478**. Clin. significant drug interactions have been predicted between ritonavir and a range of medications. In patients with HIV-1 infection, ritonavir markedly reduced viral load within 2 wk of treatment onset and also increased CD4+ cell counts. In a large placebo-controlled trial in patients with advanced HIV infection, the addn. of ritonavir to existing therapy reduced the risk of mortality by 43% and clin. progression by 56% after 6.1 mo. Triple therapy with ritonavir plus zidovudine, in combination with lamivudine or zalcitabine, reduced HIV viremia to below detectable levels in most patients with acute, and some patients with advanced HIV infection in 2 small trials. Early results suggest combination therapy with ritonavir and saquinavir increases CD4+ cell counts and decreases HIV RNA levels in patients with previously untreated HIV infection.

L14 ANSWER 5 OF 5 CAPLUS COPYRIGHT 1997 ACS
AN 1996:153437 CAPLUS
DN 124:220480
TI Retroviral protease inhibitor combinations
IN Bryant, Martin L.; Potts, Karen E.; Smidt, Mary; Tucker, Simon P.
PA G.D. Searle and Co., USA

SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
PI WO 9533464 A2 951214
DS W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-US6673 950602
PRAI US 94-253638 940603
DT Patent
LA English
AB A method is disclosed for the treatment of mammalian retrovirus infections, e.g. HIV, using combinations of retroviral protease inhibitors which are effective in preventing the replication of the retroviruses in vitro or in vivo. In particular, the invention provides protease inhibitor compds. used in combination therapy with other protease inhibitor compds. Also disclosed is combination therapy with a combination of protease inhibitors and antiviral agents other than protease inhibitors. Prepn. and activity of selected inhibitors is included.

L16 ANSWER 2 OF 5 CAPLUS COPYRIGHT 1997 ACS
AN 1997:21283 CAPLUS
DN 126:112768
TI Human immunodeficiency virus. Mutations in the viral protease that confer resistance to saquinavir increase the dissociation rate constant of the protease-saquinavir complex
AU Maschera, Barbara; Darby, Graham; Palu, Giorgio; Wright, Lois L.; Tisdale, Margaret; Myers, Richard; Blair, Edward D.; Furfine, Eric S.
CS Dep. of Molecular Biochemistry, Glaxo Wellcome, Research Triangle Park, NC, 27709, USA
SO J. Biol. Chem. (1996), 271(52), 33231-33235
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Mutations in the human immunodeficiency virus (HIV) protease (L90M, G48V, and L90M/G48V) arise when HIV is passaged in the presence of HIV protease inhibitor saquinavir. These mutations yield a virus with less sensitivity to the drug (L90M > G48V .mchgt. L90M/G48V). L90M, G48V, and L90M/G48V proteases have 1/20, 1/160, and 1/1000 the affinity for saquinavir compared to WT protease, resp. Therefore, the affinity of mutant protease for saquinavir decreased as the sensitivity of the virus to saquinavir decreased. Assocn. rate consts. for WT and mutant proteases with saquinavir were similar, ranging from 2 to 4.times.107 M-1 -1. In contrast, the dissocn. rate consts. for Wt, L90M, G48V, and L90M/G48V proteases complexed with saquinavir were 0.0014, 0.019, 0.128, and 0.54 s-1, resp. This indicated that the reduced affinity for mutant proteases and saquinavir is primarily the result of larger dissocn. rate consts. The increased dissocn. rate consts. may be the result of a decrease in the internal equil. between the bound inhibitor with the protease flaps up and the bound inhibitor with the flaps down. Interestingly, the affinity of these mutant proteases for VX-478, ABT-538, **AG-1343**, or L-735,524 was not reduced as much as that for saquinavir. Finally, the catalytic consts. of Wt and mutant proteases were detd. for eight small peptide substrates that mimic the viral cleavage sites in vivo. WT and L90M proteases had similar catalytic consts. for these substrates. In contrast, G48V and L90M/G48V proteases had catalytic efficiency (kcat/Km) values with TLNF-PISP, RKIL-FLDG, and AETF-YVDG that were 1/10 to 1/20 the value of WT protease. The decreased catalytic efficiencies were primarily the result of increased Km values. Thus, mutations in the protease decrease the affinity of the enzyme for saquinavir and the catalytic efficiency with peptide substrates.

L16 ANSWER 3 OF 5 CAPLUS COPYRIGHT 1997 ACS
AN 1996:693923 CAPLUS
DN 126:114991
TI Expression, characterization, and mutagenesis of the aspartic proteinase from equine infectious anemia virus
AU Powell, David J.; Bur, Daniel; Wlodawer, Alexander; Gustchina, Alla; Payne, Susan L.; Dunn, Ben M.; Kay, John
CS College Cardiff, Univ. Wales, Cardiff, CF1 3US, UK
SO Eur. J. Biochem. (1996), 241(2), 664-674
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English
AB The gene encoding the proteinase from equine infectious anemia virus (EIAV) was cloned and expressed in Escherichia coli. The

recombinant EIAV proteinase was purified to homogeneity and shown to have the ability to process polyprotein and synthetic peptide substrates of human immunodeficiency virus (HIV) origin with an efficiency that can approach that exhibited by HIV proteinase. EIAV proteinase, however, was not susceptible to inhibition by a wide variety of inhibitors HIV-1 proteinase, including those which have been licensed as anti-AIDS drugs. In this respect, EIAV proteinase behaves like an extreme case of a drug-resistant mutant of HIV-1 proteinase that has arisen under selective drug pressure. Only one potent inhibitor (HBY-793) of HIV-1 proteinase showed comparable efficiency against the EIAV enzyme; the compds. A-77003 and A-76889, which differ only in their stereochem. and which are otherwise structurally identical to HBY-793 from residues P2 to P2' [nomenclature of Schechter, I. & Berger, A. (1967) Biochem. Biophys. Res. Commun. 27, 157-162], were not effective inhibitors of EIAV proteinase. Mutant forms of EIAV proteinase (Thr30.fwdarw.Asp and Ile54.fwdarw.Gly) were generated and their ability to interact with substrates and inhibitors was characterized. HBY-793 inhibited [Gly54]proteinase as effectively as the wild-type proteinase but was tenfold less potent against [Asp30]proteinase. Data interpretations are presented, based on the structure solved for the complex between HBY-793 and EIAV [Gly54]proteinase [Gustchina A., Kervinen, J., Powell, D. J., Zdanov, A., Kay, J. & Wlodawer, A. (1996) Protein Sci. 5, 1453-1465].

L16 ANSWER 4 OF 5 CAPLUS COPYRIGHT 1997 ACS
AN 1996:228484 CAPLUS
DN 124:290277
TI HIV protease inhibitor combinations.
IN Barrish, Joel C.; Colonno, Richard J.; Lin, Pin-Fang M.
PA Bristol-Myers Squibb Co., USA
SO Eur. Pat. Appl., 29 pp.
CODEN: EPXXDW
PI EP 691345 A2 960110
DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
AI EP 95-304718 950705
PRAI US 94-270614 940705
US 95-436868 950517
DT Patent
LA English
AB A product comprising HIV-1 protease inhibitor (I) (BMS-186318) and .gtoreq.1 of RO 31-8959, SC-52151, A-77003, A-80987, ABT-538, L-735,524, and **AG-1343** is claimed. The combinations may eliminate or substantially reduce viral cross-resistance seen with use of individual HIV-1 protease inhibitors. A synthesis of I via coupling of epoxide (II) with aminoalc. (III) is given.

L16 ANSWER 5 OF 5 CAPLUS COPYRIGHT 1997 ACS
AN 1996:153437 CAPLUS
DN 124:220480
TI Retroviral protease inhibitor combinations
IN Bryant, Martin L.; Potts, Karen E.; Smidt, Mary; Tucker, Simon P.
PA G.D. Searle and Co., USA
SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
PI WO 9533464 A2 951214
DS W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-US6673 950602
PRAI US 94-253638 940603

DT Patent
LA English
AB A method is disclosed for the treatment of mammalian retrovirus infections, e.g. HIV, using combinations of retroviral protease inhibitors which are effective in preventing the replication of the retroviruses in vitro or in vivo. In particular, the invention provides protease inhibitor compds. used in combination therapy with other protease inhibitor compds. Also disclosed is combination therapy with a combination of protease inhibitors and antiviral agents other than protease inhibitors. Prepn. and activity of selected inhibitors is included.

L23 ANSWER 2 OF 2 CAPLUS COPYRIGHT 1997 ACS
AN 1996:228484 CAPLUS
DN 124:290277
TI HIV protease inhibitor combinations.
IN Barrish, Joel C.; Colonno, Richard J.; Lin, Pin-Fang M.
PA Bristol-Myers Squibb Co., USA
SO Eur. Pat. Appl., 29 pp.
CODEN: EPXXDW
PI EP 691345 A2 960110
DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
AI EP 95-304718 950705
PRAI US 94-270614 940705
US 95-436868 950517
DT Patent
LA English
AB A product comprising HIV-1 protease inhibitor (I) (**BMS-186318**) and .gtoreq.1 of RO 31-8959, SC-52151, A-77003, A-80987, ABT-538, L-735,524, and AG-1343 is claimed. The combinations may eliminate or substantially reduce viral cross-resistance seen with use of individual HIV-1 protease inhibitors. A synthesis of I via coupling of epoxide (II) with aminoalc. (III) is given.

L25 ANSWER 2 OF 4 CAPLUS COPYRIGHT 1997 ACS
AN 1996:601709 CAPLUS
DN 125:238651
TI Use of quinoxalines and protease inhibitors in a composition for the treatment of AIDS and/or HIV infections
IN Paessens, Arnold; Blunck, Martin; Riess, Guenther; Kleim, Joerg-Peter; Roesner, Manfred
PA Bayer A.-G., Germany
SO Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
PI EP 728481 A2 960828
DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
AI EP 96-102129 960214
PRAI DE 95-19506742 950227
DT Patent
LA German
OS MARPAT 125:238651
AB Combinations of a quinoxaline deriv. [I; R1 = halo, OH, NO2, (substituted) amino, N3, CF3, CF3O, C1-8 alkyl, CN, (substituted) Ph, N-heterocyclyl, etc.; R2, R5 = H, OH, C1-6 alkoxy, aryloxy, C1-6 acyloxy, CN, (substituted) amino, (substituted) C1-8 alkyl, (substituted) C2-8 alkenyl, (substituted) C3-8 alkynyl, (substituted) C3-8 cycloalk(en)yl, etc.; R3, R4 = H, (substituted) C1-8 alkyl, (substituted) C2-8 alkenyl, (substituted) C3-8 cycloalk(en)yl, (substituted)aryl, etc.; or R3R4 or R3R5 complete a (substituted) ring; X = O, S, Se, NR2; n = 0-4] and a peptidomimetic protease inhibitor are useful for treatment of HIV infections and AIDS. Thus, I [R1 = 6-MeO, R2 = R3 = H, R4 = (S)-MeSCH2, R5 = i-PrO2C, X = S] (0.7-6 nM) and saquinavir (6-50 nM) synergistically inhibited syncytium formation in HIV-infected human lymphocytes in vitro.

L25 ANSWER 3 OF 4 CAPLUS COPYRIGHT 1997 ACS
AN 1996:228484 CAPLUS
DN 124:290277
TI HIV protease inhibitor combinations.
IN Barrish, Joel C.; Colonno, Richard J.; Lin, Pin-Fang M.
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SO Eur. Pat. Appl., 29 pp.
CODEN: EPXXDW
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DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
AI EP 95-304718 950705
PRAI US 94-270614 940705
US 95-436868 950517
DT Patent
LA English
AB A product comprising HIV-1 protease inhibitor (I) (BMS-186318) and .gtoreq.1 of RO 31-8959, **SC-52151**, A-77003, A-80987, ABT-538, L-735,524, and AG-1343 is claimed. The combinations may eliminate or substantially reduce viral cross-resistance seen with use of individual HIV-1 protease inhibitors. A synthesis of I via coupling of epoxide (II) with aminoalc. (III) is given.

L25 ANSWER 4 OF 4 CAPLUS COPYRIGHT 1997 ACS
AN 1996:124703 CAPLUS

DN 124:196942

TI Design, synthesis, and resistance patterns of MP-134 and MP-167, two novel inhibitors of HIV type 1 protease

AU Mo, Hongmei; Markowitz, Martin; Majer, Pavel; Burt, Stanley K.; Gulnik, Sergei V.; Suvorov, Leonard I.; Erickson, John W.; Ho, David D.

CS School Medicine, New York University, New York, NY, 10016, USA

SO AIDS Res. Hum. Retroviruses (1996), 12(1), 55-61
CODEN: ARHRE7; ISSN: 0889-2229

DT Journal

LA English

AB Inhibitors of HIV-1 protease represent a new class of antiretroviral compds. This report describes the design and synthesis of 2 novel C2 symmetry-based inhibitors, MP-134 (I) and MP-167 (II), specifically targeted against HIV-1 variants with reduced sensitivity to another related protease inhibitor, A-77003. In addn., the in vitro selection of viral variants with reduced sensitivity to these 2 protease inhibitors is described. An isoleucine-to-valine substitution at residue 84 (I84V) of the HIV-1 protease confers resistance to MP-134, whereas a glycine-to-valine substitution at residue 48 (G48V) confers resistance to MP-167. Testing other protease inhibitors against these variants has revealed specific overlapping patterns of resistance among these agents. These findings have important implications in the design of combination regimens using multiple protease inhibitors and underscore the need to develop non-cross-resistant compds. to be used toward this goal.

L27 ANSWER 2 OF 4 CAPLUS COPYRIGHT 1997 ACS
AN 1996:693923 CAPLUS
DN 126:114991
TI Expression, characterization, and mutagenesis of the aspartic proteinase from equine infectious anemia virus
AU Powell, David J.; Bur, Daniel; Wlodawer, Alexander; Gustchina, Alla; Payne, Susan L.; Dunn, Ben M.; Kay, John
CS College Cardiff, Univ. Wales, Cardiff, CF1 3US, UK
SO Eur. J. Biochem. (1996), 241(2), 664-674
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English
AB The gene encoding the proteinase from equine infectious anemia virus (EIAV) was cloned and expressed in Escherichia coli. The recombinant EIAV proteinase was purified to homogeneity and shown to have the ability to process polyprotein and synthetic peptide substrates of human immunodeficiency virus (HIV) origin with an efficiency that can approach that exhibited by HIV proteinase. EIAV proteinase, however, was not susceptible to inhibition by a wide variety of inhibitors HIV-1 proteinase, including those which have been licensed as anti-AIDS drugs. In this respect, EIAV proteinase behaves like an extreme case of a drug-resistant mutant of HIV-1 proteinase that has arisen under selective drug pressure. Only one potent inhibitor (HBY-793) of HIV-1 proteinase showed comparable efficiency against the EIAV enzyme; the compds. A-77003 and A-76889, which differ only in their stereochem. and which are otherwise structurally identical to HBY-793 from residues P2 to P2' [nomenclature of Schechter, I. & Berger, A. (1967) Biochem. Biophys. Res. Commun. 27, 157-162], were not effective inhibitors of EIAV proteinase. Mutant forms of EIAV proteinase (Thr30.fwdarw.Asp and Ile54.fwdarw.Gly) were generated and their ability to interact with substrates and inhibitors was characterized. HBY-793 inhibited [Gly54]proteinase as effectively as the wild-type proteinase but was tenfold less potent against [Asp30]proteinase. Data interpretations are presented, based on the structure solved for the complex between HBY-793 and EIAV [Gly54]proteinase [Gustchina A., Kervinen, J., Powell, D. J., Zdanov, A., Kay, J. & Wlodawer, A. (1996) Protein Sci. 5, 1453-1465].

L27 ANSWER 3 OF 4 CAPLUS COPYRIGHT 1997 ACS
AN 1996:601709 CAPLUS
DN 125:238651
TI Use of quinoxalines and protease inhibitors in a composition for the treatment of AIDS and/or HIV infections
IN Paessens, Arnold; Blunck, Martin; Riess, Guenther; Kleim, Joerg-Peter; Roesner, Manfred
PA Bayer A.-G., Germany
SO Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
PI EP 728481 A2 960828
DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
AI EP 96-102129 960214
PRAI DE 95-19506742 950227
DT Patent
LA German
OS MARPAT 125:238651
AB Combinations of a quinoxaline deriv. [I; R1 = halo, OH, NO2, (substituted) amino, N3, CF3, CF3O, C1-8 alkyl, CN, (substituted)

Ph, N-heterocyclyl, etc.; R2, R5 = H, OH, C1-6 alkoxy, aryloxy, C1-6 acyloxy, CN, (substituted) amino, (substituted) C1-8 alkyl, (substituted) C2-8 alkenyl, (substituted) C3-8 alkynyl, (substituted) C3-8 cycloalk(en)yl, etc.; R3, R4 = H, (substituted) C1-8 alkyl, (substituted) C2-8 alkenyl, (substituted) C3-8 cycloalk(en)yl, (substituted)aryl, etc.; or R3R4 or R3R5 complete a (substituted) ring; X = O, S, Se, NR2; n = 0-4] and a peptidomimetic protease inhibitor are useful for treatment of HIV infections and AIDS. Thus, I [R1 = 6-MeO, R2 = R3 = H, R4 = (S)-MeSCH2, R5 = i-PrO2C, X = S] (0.7-6 nM) and saquinavir (6-50 nM) synergistically inhibited syncytium formation in HIV-infected human lymphocytes in vitro.

L27 ANSWER 4 OF 4 CAPLUS COPYRIGHT 1997 ACS
AN 1995:683314 CAPLUS
DN 123:102100
TI Kinetic Characterization and Cross-Resistance Patterns Of HIV-1 Protease Mutants Selected under Drug Pressure
AU Gulnik, Sergei V.; Suvorov, Leonid I.; Liu, Beishan; Yu, Betty; Anderson, Barry; Mitsuya, Hiroaki; Erickson, John W.
CS Frederick Cancer Research and Development Center, National Cancer Institute, Frederick, MD, 21702-1201, USA
SO Biochemistry (1995), 34(29), 9282-7
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
OS CJACS
AB Eleven different recombinant, drug-resistant HIV-1 protease (HIV PR) mutants-R8Q, V32I, M46I, V82A, V82F, V82I, I84V, V32I/I84V, M46I/V82F, M46I/I84V, and V321/K45I/F53L/A71V/I84V/L89M-were generated on the basis of results of in vitro selection expts. using the inhibitors A-77003, A-84538, and **KNI-272**. Kinetic parameters of mutant and wild-type (WT) enzymes were measured along with inhibition consts. (Ki) toward the inhibitors A-77003, A-84538, **KNI-272**, L-735,524, and Ro31-8959. The catalytic efficiency, kcat/Km, for the mutants decreased relative to WT by a factor of 1.2-15 and was mainly due to the elevation of Km. The effects of specific mutations on Ki values were unique with respect to both inhibitor and mutant enzyme. A new property, termed vitality, defined as the ratio (Kikcat/Km)mutant/(Kikcat/Km)WT was introduced to compare the selective advantage of different mutants to an inhibitor. High vitality values were generally obsd. with mutations that emerged during in vitro selection studies. The kinetic model along with the panel of mutants described here should be useful for evaluating and predicting patterns of resistance for HIV PR inhibitors and may aid in the selection of inhibitor combinations to combat drug resistance.

Thiazoles: PD, pharmacology
CN EC 3.4.23.- (HIV Protease); 0 (A 84538); 0 (Carbamates); 0 (**HIV Protease Inhibitors**); 0 (Isoquinolines); 0 (Methylurea Compounds); 0 (Oligopeptides); 0 (Pyridines); 0 (Quinolines); 0 (Recombinant Proteins); 0 (Thiazoles)

L30 ANSWER 24 OF 30 MEDLINE
ACCESSION NUMBER: 95223965 MEDLINE
TITLE: ABT-538 is a potent inhibitor of human immunodeficiency virus protease and has high oral bioavailability in humans.
AUTHOR: Kempf D J; Marsh K C; Denissen J F; McDonald E; Vasavanonda S; Flentge C A; Green B E; Fino L; Park C H; Kong X P; et al
CORPORATE SOURCE: Department of Anti-Infective Research, Abbott Laboratories, Abbott Laboratories, Abbott Park, IL 60064, USA.
CONTRACT NUMBER: AI 27720 (NIAID)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Mar 28) 92 (7) 2484-8.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 9507

AB Examination of the structural basis for antiviral activity, oral pharmacokinetics, and hepatic **metabolism** among a series of symmetry-based inhibitors of the human immunodeficiency virus (HIV) protease led to the discovery of ABT-538, a promising experimental drug for the therapeutic intervention in acquired immunodeficiency syndrome (AIDS). ABT-538 exhibited potent in vitro activity against laboratory and clinical strains of HIV-1 [50% effective concentration (EC50) = 0.022-0.13 microM] and HIV-2 (EC50 = 0.16 microM). Following a single 10-mg/kg oral dose, plasma concentrations in rat, dog, and monkey exceeded the in vitro antiviral EC50 for > 12 h. In human trials, a single 400-mg dose of ABT-538 displayed a prolonged absorption profile and achieved a peak plasma concentration in excess of 5 micrograms/ml. These findings demonstrate that high oral bioavailability can be achieved in humans with peptidomimetic inhibitors of HIV protease.
AB Examination of the structural basis for antiviral activity, oral pharmacokinetics, and hepatic **metabolism** among a series of symmetry-based inhibitors of the human immunodeficiency virus (HIV) protease led to the discovery of ABT-538, a promising experimental drug for the therapeutic intervention in acquired immunodeficiency syndrome (AIDS). ABT-538 exhibited potent in vitro activity against laboratory and clinical strains of HIV-1 [50% effective concentration (EC50) = 0.022-0.13 microM] and HIV-2 (EC50 = 0.16 microM). Following a single 10-mg/kg oral dose, plasma concentrations in rat, dog, and monkey exceeded the in vitro antiviral EC50 for > 12 h. In human trials, a single 400-mg dose of ABT-538 displayed a prolonged absorption profile and achieved a peak plasma concentration in excess of 5 micrograms/ml. These findings demonstrate that high oral bioavailability can be achieved in humans with peptidomimetic inhibitors of HIV protease.
CT Check Tags: Animal; Comparative Study; Female; Human; Male; Support,

U.S. Gov't, P.H.S.
Administration, Oral
Antiviral Agents: AD, administration & dosage
*Antiviral Agents: PK, pharmacokinetics
Bile: ME, metabolism
Bile Ducts: PH, physiology
Binding Sites
Biological Availability
Capsules
HIV Protease: CH, chemistry
HIV Protease Inhibitors: AD, administration & dosage
***HIV Protease Inhibitors: PK, pharmacokinetics**
HIV-1: DE, drug effects
HIV-2: DE, drug effects
Injections, Intravenous
Macaca fascicularis
Metabolic Clearance Rate
Models, Molecular
Molecular Structure
Pyridines: AD, administration & dosage
Pyridines: PK, pharmacokinetics
Rats
Rats, Sprague-Dawley
Tablets
Thiazoles: AD, administration & dosage
Thiazoles: PD, pharmacology
*Thiazoles: PK, pharmacokinetics
Tissue Distribution
*Valine: AA, analogs & derivatives
Valine: AD, administration & dosage
Valine: PD, pharmacology
Valine: PK, pharmacokinetics

CN EC 3.4.23.- (HIV Protease); 0 (**A 80987**); 0 (Antiviral Agents); 0 (Capsules); 0 (**HIV Protease Inhibitors**); 0 (Pyridines); 0 (Ritonavir); 0 (Tablets); 0 (Thiazoles)

L30 ANSWER 25 OF 30 MEDLINE
ACCESSION NUMBER: 95190985 MEDLINE
TITLE: Characterization of a human immunodeficiency virus type 1 variant with reduced sensitivity to an aminodiol protease inhibitor.
AUTHOR: Patick A K; Rose R; Greytok J; Bechtold C M; Hermsmeier M A; Chen P T; Barrish J C; Zahler R; Colonno R J; Lin P F
CORPORATE SOURCE: Department of Virology, Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, Connecticut 06492.
SOURCE: JOURNAL OF VIROLOGY, (1995 Apr) 69 (4) 2148-52. Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 9506
AB Development of viral resistance to the aminodiol human immunodeficiency virus (**HIV**) **protease inhibitor** BMS 186,318 was studied by serial passage of HIV

type 1 RF in MT-2 cells in the presence of increasing concentrations of compound. After 11 passages, an HIV variant that showed a 15-fold increase in 50% effective dose emerged. This HIV variant displays low-level cross-resistance to the C2 symmetric inhibitor **A -77003** but remains sensitive to the protease inhibitors Ro 31-8959 and SC52151. Genetic analysis of the protease gene from a drug-resistant variant revealed an Ala-to-Thr change at amino acid residue 71 (A71T) and a Val-to-Ala change at residue 82 (V82A). To determine the effects of these mutations on protease and virus drug susceptibility, recombinant protease and proviral HIV type 1 clones containing the single mutations A71T and V82A or double mutation A71T/V82A were constructed. Subsequent drug sensitivity assays on the mutant proteases and viruses indicated that the V82A substitution was responsible for most of the resistance observed. Further genotypic analysis of the protease genes from earlier passages of virus indicated that the A71T mutation emerged prior to the V82A change. Finally, the level of resistance did not increase following continued passage in increasing concentrations of drug, and the resistant virus retained its drug susceptibility phenotype 34 days after drug withdrawal.

AB Development of viral resistance to the aminodiol human immunodeficiency virus (**HIV**) **protease inhibitor** BMS 186,318 was studied by serial passage of HIV type 1 RF in MT-2 cells in the presence of increasing concentrations of compound. After 11 passages, an HIV variant that showed a 15-fold increase in 50% effective dose emerged. This HIV variant displays low-level cross-resistance to the C2 symmetric inhibitor **A -77003** but remains sensitive to the protease inhibitors Ro 31-8959 and SC52151. Genetic analysis of the protease gene from a drug-resistant variant revealed an Ala-to-Thr change at amino acid residue 71 (A71T) and a Val-to-Ala change at residue 82 (V82A). To determine the effects of these mutations on protease and virus drug susceptibility, recombinant protease and proviral HIV type 1 clones containing the single mutations A71T and V82A or double mutation A71T/V82A were constructed. Subsequent drug sensitivity assays on the mutant proteases and viruses indicated that the V82A substitution was responsible for most of the resistance observed. Further genotypic analysis of the protease genes from earlier passages of virus indicated that the A71T mutation emerged prior to the V82A change. Finally, the level of resistance did not increase following continued passage in increasing concentrations of drug, and the resistant virus retained its drug susceptibility phenotype 34 days after drug withdrawal.

CT Check Tags: Human
Amino Acid Sequence
Base Sequence
*Carbamates: PD, pharmacology
Cell Line
Drug Resistance, Microbial
DNA Primers
*Ethanolamines: PD, pharmacology
Hela Cells
HIV Protease: ME, metabolism
***HIV Protease Inhibitors: PD, pharmacology**
*HIV-1: DE, drug effects
HIV-1: EN, enzymology
HIV-1: GE, genetics
Molecular Sequence Data

Sequence Homology, Amino Acid
Serial Passage
Variation (Genetics)
CN EC 3.4.23.- (HIV Protease); 0 (BMS 186318); 0 (Carbamates); 0 (DNA Primers); 0 (Ethanolamines); 0 (**HIV Protease Inhibitors**)

L30 ANSWER 26 OF 30 BIOSIS COPYRIGHT 1997 BIOSIS
ACCESSION NUMBER: 97:152602 BIOSIS
DOCUMENT NUMBER: 99451805
TITLE: Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir.
AUTHOR(S): Kempf D J; Marsh K C; Kumar G; Rodrigues A D; Denissen J J; McDonald E; Kukulka M J; Hsu A; Granneman G R; Baroldi P A; Sun E; Pizzuti D; Plattner J J; Norbeck D W; Leonard J M
CORPORATE SOURCE: D-47D, AP-9A, Abbott Lab., 100 Abbott Park Rd., Abbott Park, IL 60064, USA
SOURCE: Antimicrobial Agents and Chemotherapy 41 (3). 1997. 654-660. ISSN: 0066-4804
LANGUAGE: English
AB Coadministration with the human immunodeficiency virus (**HIV**) **protease inhibitor** ritonavir was investigated as a method for enhancing the levels of other peptidomimetic **HIV protease inhibitors** in plasma. In rat and human liver microsomes, ritonavir potently inhibited the cytochrome P450 (CYP)-mediated **metabolism** of saquinavir, indinavir, nelfinavir, and **VX-478**. The structural features of ritonavir responsible for CYP binding and inhibition were examined. Coadministration of other protease inhibitors with ritonavir in rats and dogs produced elevated and sustained plasma drug levels 8 to 12 h after a single dose. Drug exposure in rats was elevated by 8- to 46-fold. A gt 50-fold enhancement of the concentrations of saquinavir in plasma was observed in humans following a single codose of ritonavir (600 mg) and saquinavir (200 mg). These results indicate that ritonavir can favorably alter the pharmacokinetic profiles of other protease inhibitors. Combination regimens of ritonavir and other protease inhibitors may thus play a role in the treatment of HIV infection. Because of potentially substantial drug level increases, however, such combinations require further investigation to establish safe regimens for clinical use.
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regimens of ritonavir and other protease inhibitors may thus play a role in the treatment of HIV infection. Because of potentially substantial drug level increases, however, such combinations require further investigation to establish safe regimens for clinical use.

ST RESEARCH ARTICLE; HUMAN IMMUNODEFICIENCY VIRUS; HUMAN; PHARMACOLOGY; ENZYMOLOGY; PROTEASE; RITONAVIR; ANTIVIRAL-DRUG; PLASMA; LIVER MICROSOME; CYTOCHROME P450; SAQUINAVIR; ENZYME INHIBITOR-DRUG; ANTIVIRAL-DRUG; PHARMACOKINETICS; PHARMACOKINETIC ENHANCEMENT; INDINAVIR; ANTIVIRAL-DRUG; ENZYME INHIBITOR-DRUG; NELFINAVIR; ANTIVIRAL-DRUG; ENZYME INHIBITOR-DRUG; **VX-478**; ENZYME INHIBITOR-DRUG; ANTIVIRAL-DRUG; SAFE COMBINATION REGIMENS; BLOOD AND LYMPHATICS; DIGESTIVE SYSTEM

L30 ANSWER 27 OF 30 BIOSIS COPYRIGHT 1997 BIOSIS
ACCESSION NUMBER: 96:4037 BIOSIS
DOCUMENT NUMBER: 98576172
TITLE: Hepatic and intestinal **metabolism** of **MK-639**, an **HIV protease inhibitor**, in rats and human.
AUTHOR(S): Hensleigh M; Chiba M; Lin J H
CORPORATE SOURCE: Dep. Drug Metabolism, Merck Res. Lab., West Point, PA 19486, USA
SOURCE: Annual Meeting of the American Association of Pharmaceutical Scientists, Miami Beach, Florida, USA, November 5-9, 1995. Pharmaceutical Research (New York) 12 (9 SUPPL.). 1995. S374. ISSN: 0724-8741
DOCUMENT TYPE: Conference
LANGUAGE: English
TI Hepatic and intestinal **metabolism** of **MK-639**, an **HIV protease inhibitor**, in rats and human.

L30 ANSWER 28 OF 30 BIOSIS COPYRIGHT 1997 BIOSIS
ACCESSION NUMBER: 94:8709 BIOSIS
DOCUMENT NUMBER: 97021709
TITLE: **Metabolism** and disposition of the **HIV protease inhibitor A-77003**.
AUTHOR(S): Denissen J F; Marsh K; Grabowski B; Johnson M
CORPORATE SOURCE: Abbott Lab., Abbott Park, IL 60064, USA
SOURCE: AAPS (American Association of Pharmaceutical Scientists) Eighth Annual Meeting and Exposition, Orlando, Florida, USA, November 14-18, 1993. Pharmaceutical Research (New York) 10 (10 SUPPL.). 1993. S376. ISSN: 0724-8741
DOCUMENT TYPE: Conference
LANGUAGE: English
TI **Metabolism** and disposition of the **HIV protease inhibitor A-77003**.
ST MEETING ABSTRACT; DOG; RAT; HUMAN IMMUNODEFICIENCY VIRUS; **A-77003**; ANTIVIRAL-DRUG; ENZYME INHIBITOR-DRUG; PHARMACOKINETICS

L30 ANSWER 29 OF 30 USPATFULL
ACCESSION NUMBER: 97:37235 USPATFULL
TITLE: **HIV protease**

inhibitor combinations

INVENTOR(S): Barrish, Joel C., 46 Heather Valley Rd., Holland, PA, United States 18966
Colonno, Richard J., 5288 Lower Mountain Rd., Buckingham, PA, United States 18938
Lin, Pin-Fang M., 169 Northford Rd., Branford, CT, United States 06405

	NUMBER	DATE
PATENT INFORMATION:	US 1649	970506
APPLICATION INFO.:	US 95-436868	950517 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 94-270614, filed on 5 Jul 1994 which is a continuation-in-part of Ser. No. US 87-79978, filed on 31 Jul 1987, now patented, Pat. No. US 4987228, issued on 22 Jan 1991
DOCUMENT TYPE: Statutory
PRIMARY EXAMINER: Jordan, Charles T.
ASSISTANT EXAMINER: Chelliah, Meena
LEGAL REPRESENTATIVE: Morse, David M.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 692
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Combinations of certain HIV-1 protease inhibitors are provided which effectively inhibit the HIV-1 protease enzyme while eliminating or substantially reducing the viral cross-resistance seen with use of individual HIV-1 protease inhibitors. Such combinations are useful in the treatment of diseases associated with the AIDS virus.

TI **HIV protease inhibitor** combinations

SUMM EP 402646 A1 discloses the Abbott HIV-1 protease inhibitor designated **A-77003** having the formula ##STR9## and the chemical name (2S,3R,4S,5S)-2,5-di-(N-((N-methyl-N-((2-pyridinyl)methyl)amino)carbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

SUMM EP 486948 A2 discloses the Abbott HIV-1 protease inhibitor designated **A-80987** having the formula ##STR11## and the chemical name (2S,3S,5S)-2-(N-(N-((2-pyridinyl)methoxycarbonyl)-valinyl)amino)-5-(N-((3-pyridinyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

SUMM Various suggestions have been made in the literature to combine antiviral drugs, including **HIV protease inhibitors**, with other antiviral agents (see, for example, Antimicrob. Agents Chemother. 36(3), 509-520, 1992; J. Acquired Immune Deficiency Syndromes, 3 (Suppl. 2), S99-S103, 1990; and J. Acquired Immune Deficiency Syndromes, 6, 162-170, 1993). PCT Application WO 94/02149 discloses the so-called convergent combination approach to antiviral therapy whereby an antivirally effective amount of three or more different agents are employed, each of which is capable of inhibiting the activity of the same gene product or gene of a virus.

SUMM Suppressing chronic HIV infection requires long-term therapy. We have found that although the HIV virus appears to have more

difficulty becoming resistant to protease inhibitors than to non-nucleoside reverse transcriptase inhibitors, resistance eventually does develop to **HIV protease inhibitors**. In-vitro drug sensitivity assays on the HIV-1 protease inhibitors currently in clinical trials have demonstrated unique resistance profiles, suggesting that combination of two or more protease inhibitors may be an effective approach to inhibiting HIV replication.

SUMM In one aspect this invention provides pharmaceutical compositions for prophylaxis or treatment of diseases caused by the HIV virus comprising an effective HIV-inhibiting amount of BMS-186318 having the formula ##STR16## or a pharmaceutically acceptable derivative thereof, and an effective HIV-inhibiting amount of one or more HIV-1 protease inhibitors selected from the group consisting of (a) Ro 31-8959 having the formula ##STR17## or a pharmaceutically acceptable derivative thereof, (b) SC-52151 having the formula ##STR18## or a pharmaceutically acceptable derivative thereof, (c) **A-77003** having the formula ##STR19## or a pharmaceutically acceptable derivative thereof, (d) **A-80987** having the formula ##STR20## or a pharmaceutically acceptable derivative thereof, (e) L-735,524 having the formula ##STR21## or a pharmaceutically acceptable derivative thereof, (f) ABT-538 having the formula ##STR22## or a pharmaceutically acceptable derivative thereof, and (g) AG-1343 having the formula ##STR23## or a pharmaceutically acceptable derivative thereof, in combination with a pharmaceutically acceptable carrier or diluent.

SUMM In another aspect the present invention provides a method for the prophylaxis or treatment of diseases caused by the HIV virus in a human patient, which comprises administering to said patient, either sequentially or concurrently, an effective HIV-inhibiting amount of BMS-186318 having the formula ##STR24## or a pharmaceutically acceptable derivative thereof, and an effective HIV-inhibiting amount of one or more HIV-1 protease inhibitors selected from (a) Ro 31-8959 having the formula ##STR25## or a pharmaceutically acceptable derivative thereof, (b) SC-52151 having the formula, ##STR26## or a pharmaceutically acceptable derivative thereof, (c) **A-77003** having the formula ##STR27## or a pharmaceutically acceptable derivative thereof, (d) **A-80987** having the formula ##STR28## or a pharmaceutically acceptable derivative thereof, (e) ABT-538 having the formula ##STR29## or a pharmaceutically acceptable derivative thereof, (f) L-735,524 having the formula ##STR30## or a pharmaceutically acceptable derivative thereof, and (g) AG-1343 having the formula ##STR31## or a pharmaceutically acceptable derivative thereof.

SUMM In yet another aspect the present invention provides a method for reducing or eliminating resistance resulting from administration of an HIV-1 protease inhibitor selected from the group consisting of (a) Ro 31-8959, or a pharmaceutically acceptable derivative thereof, (b) SC-52151, or a pharmaceutically acceptable derivative thereof, (c) **A-77003**, or a pharmaceutically acceptable derivative thereof, (d) **A-80987**, or a pharmaceutically acceptable derivative thereof, (e) ABT-538, or a pharmaceutically acceptable derivative thereof, (f) L-735,524, or a pharmaceutically acceptable derivative thereof, and (g)

AG-1343, or a pharmaceutically acceptable derivative thereof, or a combination of two or more of said inhibitors, which comprises administering either sequentially or concurrently, an effective HIV-inhibiting amount of BMS-186318, or a pharmaceutically acceptable derivative thereof.

DETD Combination therapy has been proposed for treatment of antiviral diseases, including diseases associated with AIDS. In our parent application Ser. No. 07/79978 filed Jun. 25, 1993, we disclosed that the novel aminediol HIV-1 protease inhibitors of general formula I above could be used in combination with other antiviral agents, including other **HIV protease inhibitors**.

DETD The term "a pharmaceutically acceptable derivative" as used herein is meant to include any pharmaceutically acceptable salt, prodrug or solvate of a compound of the present invention which, upon administration to the host, is capable of providing (directly or indirectly) the parent compound or an antivirally effective **metabolite** or residue thereof.

DETD Prodrugs of the HIV inhibitor compounds are also contemplated. The term "prodrug" as used herein denotes a compound which, upon administration to a patient, undergoes chemical conversion by **metabolic** or chemical processes to yield the parent compound, or a salt or solvate thereof. See H. Bundgaard, "Drugs of the Future", 16(5), 443-458 (1991) and H. Bundgaard(Ed.), "Design of Prodrugs", 1985 Elsevier (Amsterdam), both incorporated herein by reference.

DETD For example, BMS-186318 may be administered in a total daily dosage of from about 1 to 150 mg/kg of body weight, preferably about 10 to 50 mg/kg of body weight. Ro 31-8959 may be administered in a daily dosage of from about 3 mg to about 3 grams, preferably about 10 mg to 1 gram. SC-52151 may be administered in a total daily dose of from about 0.001 to 10 mg/kg body weight, preferably 0.01 to 1 mg/kg. **A-77003** may be administered in a daily dosage of from about 0.001 to 10 mg/kg, preferably 0.01 to 1 mg/kg of body weight. **A-80987** may be administered in a total daily dose of from about 0.001 to 300 mg/kg body weight, preferably 0.1 to 10 mg/kg. L-735,524 may be administered in a total daily dosage of from about 0.02 to 10 grams. ABT-538 may be administered in a total daily dosage of from about 0.001 to 300 mg/kg of body weight. AG-1343 may be administered in a total daily dosage of from about 100 mg to 2000 mg.

L30 ANSWER 30 OF 30 USPATFULL

ACCESSION NUMBER:	96:14811 USPATFULL
TITLE:	Retrocarbamate protease inhibitors
INVENTOR(S):	Barrish, Joel C., Holland, PA, United States Spergel, Steven H., Bensalem, PA, United States
PATENT ASSIGNEE(S):	Bristol-Myers Squibb Co., Princeton, NJ, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5492910	960220
APPLICATION INFO.:	US 94-341245	941117 (8)
DOCUMENT TYPE:	Utility	
PRIMARY EXAMINER:	McKane, Joseph K.	

ASSISTANT EXAMINER: Stockton, Laura L.
LEGAL REPRESENTATIVE: Davis, Stephen B.
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
LINE COUNT: 1097
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention discloses compounds of the formula ##STR1## are disclosed as **HIV protease inhibitors** .

AB The invention discloses compounds of the formula ##STR1## are disclosed as **HIV protease inhibitors** .

DETD Prodrugs and solyates of the compounds of formula I are also part of this invention. The term prodrug denotes a compound which, upon administration to a subject, undergoes chemical conversion by **metabolic** or chemical processes to yield a compound of the formula I, or a salt and/or solvate thereof. See H. Bundgaard, "Drugs of the Future", 16 (5), 443-458 (1991); and H. Bundgaard (Ed), "Design of Prodrugs" 1985 Elsevier (Amsterdam), both incorporated herein by reference.

DETD The pharmaceutical compositions of the present invention may contain an amount of the inventive compounds effective for the inhibition of retroviral replication and preferably an amount effective for the treatment and/or prevention of infection by HIV. The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes amounts such as those from about 1 to 150 mg/kg of body weight of active compound per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the **metabolic** stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination and severity of the particular condition.

DETD Other therapeutic agents may include, but are not restricted to the following: antivirals exemplified by AL-721, interferon beta, polymannoacetate, ganciclovir, DDC (dideoxycytidine), d4T, DDI (dideoxyinosine), Foscarnet (trisodium phosphonoformate), HPA-23, eflornithine, Peptide T (octapeptide sequence), Reticulose (nucleophosphoprotein), AZT, ansamycin LM 427, trimetrexate, UA-001, ribavirin, .alpha.-interferon, acyclovir, 3TC, PMEA, nevirapine, pyridinones (e.g. L-697,661), BHAPs (e.g. U-90152), alpha-APA derivatives (e.g. R 18893), TIBO derivatives (e.g. R.sub.82913, Ro 31-8959, SC 52151, **A-77003**, **A-80987**, A-84538, and L-737,524); immunomodulators exemplified by bropirimine, Ampligen (mismatched RNA), Anti-human alpha interferon antibody, Colony Stimulating Factor (GM-CSF), CL246,738, IMREG-1, IMREG-2, diethyl dithio carbamate, interleukin-2, inosine pranobex, methionine enkephalin, MTP-PE (muramyl-tripeptide), Thymypentin (TP-5) (thymic compound), recombinant erythropoietin, naltrexone, TNF (tumor necrosis factor); and antibiotics exemplified by Pentam 300 (pentamidine isethionate).

DETD In particular, the **HIV protease inhibitors** of the present invention may be used in combination with other anti-retroviral therapies for the treatment of AIDS. Such combined therapies may include, but are not limited